REVIEW

Dealing with saturated and unsaturated fatty acid metabolism for anticancer therapy

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Purpose of review
Although saturated fatty acid (FA) (SFA) and monounsaturated FA (MUFA) are synthesized in cancer cells from acetyl-CoA, polyunsaturated FAs (PUFAs) are necessarily obtained from diet. Depending on concentrations and metabolism, these different FAs may support tumor proliferation but also exert growth inhibitory effects. The mutual interplay between them also requires to integrate the FA oxidation component that may be concomitant with FA synthesis is cancer cells.

Recent findings
New molecular mechanisms driving FA synthesis, lipotoxicity and anti-inflammatory activity of eicosanoids in mouse and human cancers were recently elicited. To block or take advantage of the above represent attractive perspectives of treatments to fight cancer progression.

Summary
The various enzymatic reactions leading to SFA synthesis represent as many targets to prevent tumor growth. Ironically excess SFAs are per-se toxic for cancer cells and the introduction of a double bound to form MUFA is actually limiting lipotoxicity in cancer cells. Blocking stearoyl-CoA desaturase therefore represents another attractive modality. By contrast, dietary PUFAs may exert direct cytotoxic effects by promoting apoptosis or by generating anti-inflammatory eicosanoids. Altogether, these data point out the intricate relationship between SFA, MUFA and PUFA at the heart of the metabolism of proliferating cancer cells.

Keywords
eicosanoid, fatty acid metabolism, monounsaturated, omega-3, polyunsaturated, saturated

INTRODUCTION

The Warburg effect has drawn the focus of tumor metabolism toward glucose for decades. Fatty acids (FA) are now gaining the attention they deserve considering their role as membrane components, energy fuels and precursors of signaling molecules. FAs are either endogenously synthesized, often to a larger extent in cancer cells than in healthy cells, or captured from the extracellular medium. The latter is the only option for polyunsaturated FA (PUFA), which are considered as essential since they cannot be synthesized in humans. Here, we will summarize the most recent findings related to the synthesis and/or metabolism of these essential and nonessential FA together with the prospects of therapeutic exploitation of this knowledge.

SYNTHESIS OF SATURATED AND MONOUNSATURATED FATTY ACIDS IN TUMORS

Cancer cells require nonessential FA to support membrane formation, energy storage and signaling. The building block for FA synthesis (FAS) is acetyl-CoA that is generated from citrate (itself derived from glucose or glutamine) or acetate, upon the activity of ATP-citrate lyase (ACLY) and acyl-CoA synthetase short-chain family member (ACSS), respectively (Fig. 1). ACLY was recently documented to share some structures with citrate synthase, the first enzyme of the TCA cycle [1], further emphasizing its critical role in linking carbohydrate and lipid metabolism. Acetate largely originates from gut microbiota but was also recently reported to derive from pyruvate in the context of hyperactive glucose metabolism [2▪▪]. FAS starts with the carboxylation

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KEY POINTS

- Conversion of SFA in MUFA reduces inflammation and lipotoxicity in cancer cells.
- Cancer cells rely more on lipogenesis than healthy cells but can also capture, store and metabolize FA from the extracellular medium.
- Dietary $n-3$ PUFA is associated with a reduction in mortality from cancer but the impact of supplementary PUFA on cancer incidence is not established.
- Expression of the PUFA receptor G protein-coupled receptor 120 in the stroma but not in cancer cells accounts for antitumor effects of $n-3$ PUFA.
- Synthesis of eicosanoids (resolvins and lipoxins) from PUFA supports their anti-inflammatory effects, an antitumor pathway further accentuated by aspirin-induced cyclooxygenases acetylation.

of acetyl-CoA by acetyl-CoA carboxylase (ACC) to form malonyl-CoA which in turn condenses with new acetyl-CoA molecules through the action of the FA synthase (FASN) (Fig. 1). There are two ACC isoforms, namely cytosolic ACC1 and outer mitochondria membrane-anchored ACC2, that are finely regulated by phosphorylation and allosteric interactions. The critical role of these rate-limiting enzymes in the lipogenic pathway was recently emphasized by the identification of additional modes of regulation. ACC1 enzyme activity was indeed shown to be modulated by structural changes shifting the enzyme conformation from nonpolymeric to filament organization [3] while we documented that sirtuin-mediated histone deacetylation can lead to ACC2 downregulation in the acidic tumor compartment [4].

De novo synthesized 16-carbon palmitate [the most common saturated FA (SFA)] is subsequently elongated and/or desaturated to generate a diversity

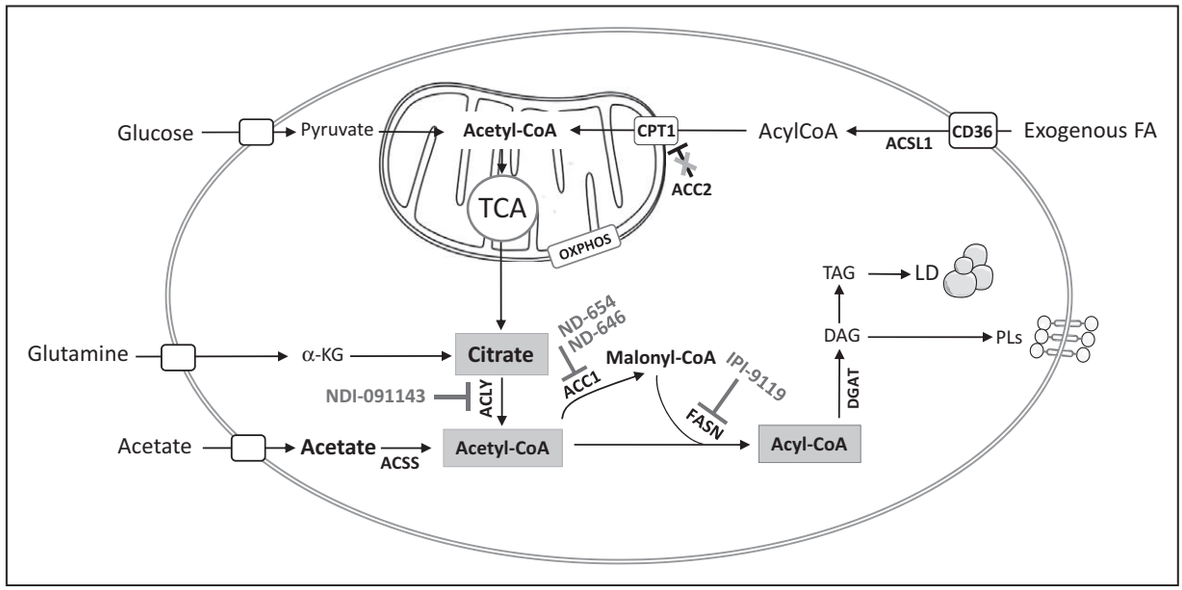

FIGURE 1. FA synthesis and oxidation pathways in cancer cells. *De novo* FA synthesis requires (glucose or glutamine-derived) citrate or (microbiota-produced) acetate conversion into acetyl-CoA *via* ATP citrate lyase (ACLY) and acyl-CoA synthetase short-chain family member (ACSS), respectively, before carboxylation *via* acetyl-CoA carboxylase (ACC) and further condensation *via* fatty acid synthase (FASN) enzymes. Extracellular fatty acids (FA) are taken up through plasma membrane transporter such as CD36, converted into acyl-CoA *via* long-chain-fatty-acid-CoA ligase 1 (ACSL1) and then transported into mitochondria *via* carnitine palmitoyl transferase-1 (CPT1). Acyl-CoA undergo mitochondrial β-oxidation (or fatty acid oxidation (FAO)) to generate acetyl-CoA and reducing equivalents that fuel the TCA cycle. ACC exist as two related enzymes, the cytosolic isoform ACC1 and the mitochondrion-anchored ACC2. Under chronic acidosis, histone deacetylation inhibits ACC2-encoding gene expression and consecutive ACC2 repression inhibits malonyl-CoA production in the mitochondria microenvironment, thereby restoring the otherwise inhibited CPT1 activity (because of FAS). In the acidic tumor compartment, FAS and FAO can thus occur concomitantly. Drugs under clinical development or used as preclinical tools are indicated. α-KG: α-ketoglutarate; PLs, phospholipid; DAG, diacylglycerol; TAG, triacylglycerol; DGAT, diacylglycerol acyltransferase; LDs, lipid droplets.

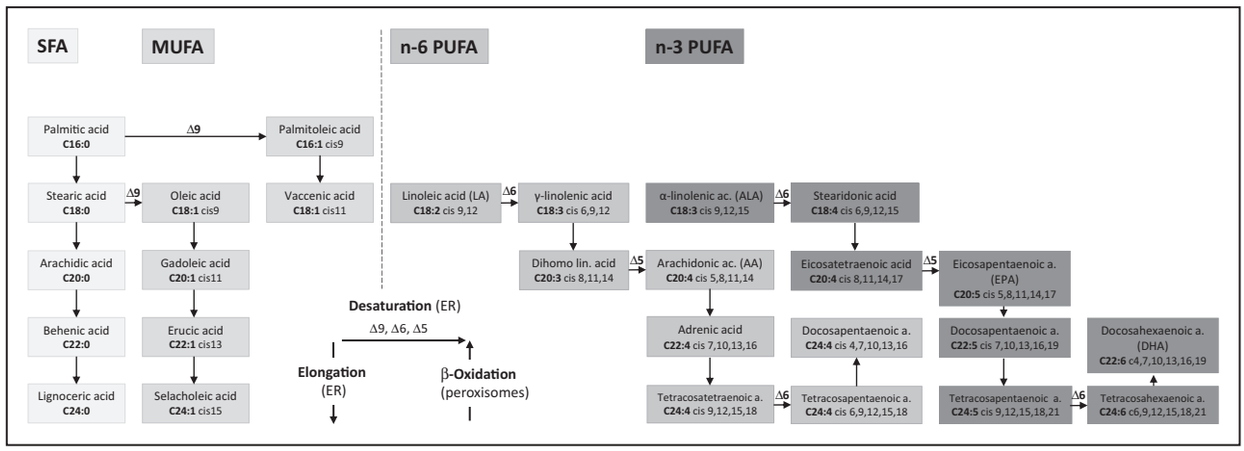

FIGURE 2. Biosynthesis of fatty acids. Scheme of major FAs, the number of carbon increasing from top to bottom and the number of double bonds increases from left to right. Palmitate is either elongated to stearic acid (18 : 0) and other long chain saturated FAs (SFA), or desaturated, together with stearic acid (18 : 0), by D9D to produce de novo monounsaturated FA (MUFA) such as palmitoleic acid (16 : 1) and oleic acid (18 : 1). As for polyunsaturated FAs (PUFA), D6D and D5D work cooperatively with elongases to introduce double bonds and extend the carbon chain in a successive manner, from ALA (18 : 3 *n* – 3) to EPA (20 : 5 *n* – 3) in the *n* – 3 series, and from LA (18 : 2 *n* – 6) to AA (20 : 4 *n* – 6) in the *n* – 6 series. EPA and AA are further elongated, desaturated, and submitted to peroxisomal β-oxidation to yield DHA (22 : 6 *n* – 3) and docosapentaenoic acid (22 : 5 *n* – 6), respectively. Of note, current dietary habits of most Western countries do not include the regular intake of *n* – 3 PUFA-rich marine-derived fishes and the current average *n* – 6/*n* – 3 ratio is around 15. This ratio is much higher than the ratio resulting from our ancestor's diet and is thought to have negative consequences for human health. ER, endoplasmic reticulum.

of FA through the action of so-called elongases and desaturases (Fig. 2). At first, stearoyl-CoA desaturase (SCD1), also named delta-9 desaturase, allows to generate monounsaturated FA (MUFA) which are a major component of plasma membrane. Resistance to SCD inhibitors however led to the discovery of an unusual metabolic pathway to produce MUFA in cancer cells under the form of sapienate [5▪]. This pathway that was so far mostly described in hair follicles where sapienate is produced by sebaceous glands, requires the enzyme FA desaturase (FADS2), also named delta-6 desaturase (D6D). Of note, inhibiting FADS2 in cancers resistant to SCD1 inhibitors may still not suffice to block cancer cell growth. The uptake of exogenous MUFA can compensate for the deficit in MUFA generation and the blockade of FADS2 may lead to alterations in the processing of PUFA (see below).

OPPOSITE ROLES OF SATURATED AND MONOUNSATURATED FATTY ACIDS

After activation by covalent modification by CoA via fatty acyl-CoA synthetases, FA can be esterified with glycerol generating phospholipids such as phosphatidylcholine and phosphatidylethanolamine (Fig. 1). The nature of phospholipids directly influences membrane fluidity which may have profound impact on cancer cell phenotype, including an increase in metastatic capacity [6]. The ratio of SFA and unsaturated FA determines the fluidity in the membrane, double bonds limiting the way lipids can pack together by putting kinks into the otherwise straightened hydrocarbon chain. SFA-driven reduction in membrane fluidity is often associated with alterations in the potential of lateral diffusion of proteins within the membrane matrix thereby reducing their capacity to interact with substrates or other proteins. Direct alterations in the activity of integral enzymes are also likely to be induced by a defect in MUFA production. Recently, Gianfrancesco *et al.* [7] observed that upon SFA uptake, intracellular acyl-CoA activates NOD-like receptor family, pyrin domain containing 3 (NLRP3) inflammasome in human macrophages. Significantly, acyl-CoA is not used for oxidation in mitochondria but instead is channeled toward phospholipids, leading to a loss of membrane fluidity mostly through saturation of phosphatidylcholine. Consecutive membrane remodeling alters the plasma membrane Na^+, K^+-ATPase, which in turn activates NLRP3 because of increased K^+ efflux [7]. Alterations in membrane fluidity therefore allows to link Western diet and obesity-induced inflammation but also support cancer progression through the maintenance of a proinflammatory environment in tumors developing in the presence of SFA overload.

The other rationale behind the need for cancer cells to convert SFA to MUFA is to reduce the intrinsic toxicity of SFA thereby maintaining proliferation. New insights on the origin of this lipotoxicity were recently unraveled by Piccolis *et al.* [8▪▪] who documented that increase in disaturated glycerolipids is associated with an endoplasmic reticulum stress response and consecutive induction of an apoptotic program. Significantly, increasing the MUFA content of the glycerol backbone reduced endoplasmic reticulum stress and protected from palmitate toxicity whereas SCD1 desaturase inhibition worsened palmitate toxicity [8▪▪]. The protective effects of unsaturated FA was also documented by Ackerman *et al.* [9] who reported that triglycerides can counter a toxic buildup of saturated lipids by releasing MUFA from lipid droplets into phospholipid pools thereby limiting the overproduction of toxic saturated ceramides and acyl-carnitines.

THERAPEUTIC TARGETING OF NONESSENTIAL FATTY ACID METABOLISM IN CANCER

In most cancers, the lipogenic enzymes are upregulated and often associated with poor prognosis. This observation led to the conclusion that while most normal cells rely on lipids obtained from the diet or those made in the liver, tumors instead synthesize FA de novo. Several strategies aiming to block lipogenic enzymes were actually reported in the last few years, including for instance inhibitors of ACLY [10], ACC [11,12] and FASN [13] (Fig. 1). The outcomes of blocking the activity of lipogenic enzymes have also considerable implications on the extent of protein acylation. Although protein (de-)acetylation regulated by the activity of lipogenic enzymes such as ACSS2 [14], ACLY [15▪] and ACC [4,16] were the first to be reported, other fatty acyl-related posttranslational modifications including malonylation [17] or crotonylation [18] only begin to be explored.

Importantly, although the inhibition of lipogenic enzymes is associated with significant antitumor effects thereby supporting a preference for FAS over fatty acid oxidation (FAO), it is now increasingly recognized that the contribution of exogenous FA to cancer cell bioenergetics is far from negligible [19]. Many tumors actually scavenge lipids from their environment, through the activity of various proteins involved in FA uptake, including FA translocase/CD36, the activity of which being critical for metastatic spreading [20▪▪,21]. Importantly, FAO and FAS are not mutually exclusive in tumors contrary to healthy tissues wherein the risk of a futile cycle within cells degrading de novo synthesized FA is prevented by the capacity of malonyl-CoA produced by ACC2 enzymes to block CPT1, the mitochondrial fatty acyl-CoA transporter. We previously reported how tumor acidosis may promote the downregulation of mitochondrial ACC2 preventing this negative feedback loop whereas cytosolic ACC1 keeps generating malonyl-CoA as a substrate for FAS [4,22,23] (Fig. 1).

SOURCES AND PRODUCTION OF ESSENTIAL POLYUNSATURATED FATTY ACID

$n-3$ and $n-6$ classes of PUFAs are named as such because the first double bond is placed either three or six carbons from the methyl end of the carbon chain, respectively. The desaturase needed to place the double bond in position $n-3$ or $n-6$ in the PUFAs is lacking in mammals and these two PUFA classes are not interconvertible. 18-Carbon PUFAs, α-linolenic acid (ALA) and linoleic acid are thus considered essential $n-3$ and $n-6$ PUFAs, respectively (Fig. 2). Metabolism of 18-carbon linoleic acid and ALA starts with the addition of a double bond (at the sixth position) by the D6D enzyme. Elongase then extends the carbon chain to yield 20–24-carbon PUFA and the delta-5 desaturase (D5D) and D6D further introduce double bonds (Fig. 2). Major long-chain $n-3$ PUFA are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Linoleic acid is also metabolized by the sequential action of several desaturases and elongases to produce for instance arachidonic acid and docosopentaenoic acid (Fig. 2). Significantly, Kim *et al.* [24] recently documented that D5D/D6D provide a mechanism for glycolytic nicotinamide adenine dinucleotide (NAD^+) recycling that supports glycolysis and cell viability when the cytosolic NAD^+/NADH (reduced form of NAD^+) ratio is reduced. These findings highlight biologic roles for D5D/D6D activity independent of their PUFA-end products and inversely stress that PUFA desaturation increases in response to a reduction in cytosolic NAD^+/NADH ratio. Although ALA affinity for D6D is higher than that of linoleic acid, linoleic acid is the predominant PUFA in the Western diet, thereby limiting the endogenous production of EPA and DHA. The main source of long-chain $n-3$ PUFA (e.g. EPA and DHA) is thus also dietary.

DIETARY POLYUNSATURATED FATTY ACID AND HUMAN CANCER

To summarize decades of experiments and trials evaluating the role of $n-3$ PUFA in cancer, one may state that beneficial effects observed in various animal tumor models did not translate in very convincing success in human studies. The levels and

sources of dietary intake of *n*3-PUFA, the possible contamination of fish oils with carcinogenic compounds but also the cancer subtype and the genetic background of the patient are usually claimed to account for discrepancies between experimental and clinical data. Recently, the relation between supplemental or dietary $n-3$ PUFA and risks of cardiovascular disease and cancer was evaluated in two very large studies. The first one is a randomized, placebo-controlled Vitamin D and Omega-3 Trial in a US cohort of more than 25 000 participants (men >50 years and women >55 years) [25]. During a median follow-up of 5.3 years, invasive cancer was diagnosed in 820 participants in the $n-3$ group (1 g/day as a fish-oil capsule containing 460 mg EPA and 380 mg DHA) and in 797 in the placebo group. No significant differences between the randomized groups were observed with regard to the incidence of breast, prostate or colorectal cancer. In a second large-scale study, intakes of various FA were assessed via food frequency questionnaires in a cohort of more than half a million North Americans aged 50–71 years with 16 years of follow-up on average [26▪▪]. The major limitation of such study is the observational setting that precludes causality demonstration. Still, the authors found consistent associations of SFA intake with higher cause-specific mortality, including cancer. In contrast, the participants with higher intake of marine $n-3$ PUFA and replacing SFA with plant MUFA or linoleic acid had lower mortality including from cancer. Conclusions of the above two studies support the assumption that a deficit in dietary PUFA (together with a SFA excess) may promote tumor growth while evidences are still lacking that PUFA supplementation may have a significant impact on cancer progression.

ANTITUMOR MECHANISMS OF ACTION OF DIETARY POLYUNSATURATED FATTY ACID

Several extensive reviews have listed the various mechanisms that could account for the beneficial effects of $n-3$ PUFA [27,28]. These pleiotropic effects mostly refer to induction of apoptotic cell death and anti-inflammatory effects with the caveat that normal cells are largely spared by $n-3$ PUFA cytotoxic activity. Among the most recent insights on the understanding of the anticancer effects of PUFA are the better characterization of PUFA receptors and eicosanoid signaling.

G protein-coupled receptor 120 (GPR120) is a *bona fide* $n-3$ PUFA receptor. Oh *et al.* [29] previously reported that GPR120 is highly expressed in adipose tissue and proinflammatory macrophages in mice fed a high-SFA diet and that addition of fish oil containing DHA and EPA exerted potent anti-inflammatory effects through this same receptor. More recently, Liang *et al.* [30▪▪] reported that host GPR120 plays a central role in the antiprostate cancer effects of dietary $n-3$ PUFA. These authors showed that in GPR120 knockout mice, $n-3$ PUFA had no anticancer effects although they inhibited GPR120 knockout-prostate tumor allografts grown in wild-type mice, suggesting an effect of $n-3$ PUFA on stromal cells. This was confirmed in human tissue, higher expression of stromal GPR120 correlated with greater reduction in expression of cell cycle progression genes in men with prostate cancer on a high $n-3$ PUFA diet [30▪▪]. In mice, the authors identified M2-like tumor-associated macrophages as the most likely targets of $n-3$ PUFA. Further investigations are needed to determine whether host GPR120 expression and/or activation has the potential to predict anticancer effects of dietary $n-3$ PUFA in cancer patients.

The term eicosanoids is used to describe oxidation products of 20-carbon PUFA (such as arachidonic acid and EPA) and their metabolites [31]. The first step in eicosanoid metabolism requires their release from cell membrane phospholipids under the action of phospholipase A2 (PLA2). Subsequently, free PUFA are oxidized by different enzymes, including cyclooxygenases (COX) and lipoxygenases (LOX) to generate eicosanoid molecules including prostaglandins and thromboxanes [31] (Fig. 3). Importantly, upon acetylation by aspirin, COX2 gains a new catalytic activity and shifts from proinflammatory autacoid production toward lipoxin (also termed aspirin-triggered lipoxin) from arachidonic acid and resolvins from $n-3$ PUFA, both associated with anti-inflammatrory effects [32]. Arachidonic acid, EPA and DHA are the most abundant PUFA incorporated in cell membranes. The selectivity of different PLA2 isoforms influences the nature of the PUFA release and the expression levels of COX and LOX isoforms account for different patterns of eicosanoid release according to tumor types. Recent evidence obtained by several labs have identified lipid autacoids as key players in the so-called Revesz effect [33] that describes how the rate of tumor growth may be increased by mixing lethally irradiated cancer cells (including proinflammatory cell debris) to an inoculum of viable tumor cells. Sulciner *et al.* [34▪▪] recently documented that tumor cells killed by chemotherapy or targeted therapy could stimulate primary tumor growth by triggering macrophage release of proinflammatory cytokines/chemokines after phosphatidylserine exposure. This phenomenon was inhibited by anti-inflammatory and proresolving

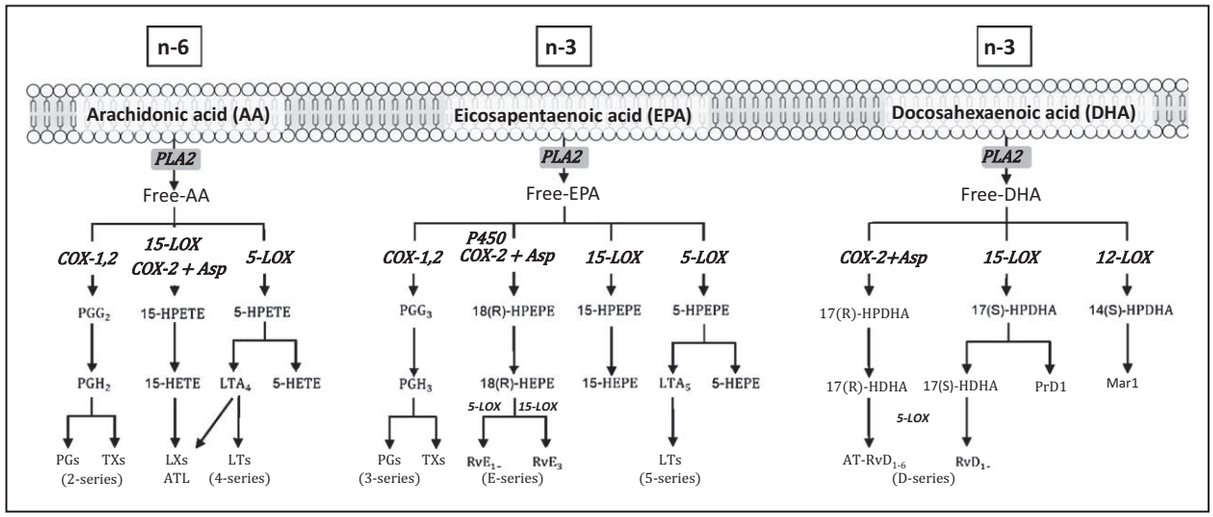

FIGURE 3. Main eicosanoid biosynthesis pathways. First step for ~~eicosanosid~~ metabolism is their release from phospholipids by the action of phospholipase A2 (PLA2) enzymes. After the release of AA from n – 6 PUFA, and EPA and DHA from n – 3 PUFA, cyclooxygenase (COX1/2), lipoxygenase (LOX, mainly 5-LOX, 12-LOX, 15-LOX) and cytochrome P450 epoxygenase enzymes are the main enzymes involved in the production of the different eicosanoids. The major eicosanoids are prostaglandins (PG), thromboxanes (TX), and leukotrienes (LT); generally those obtained from *n* – 6 PUFA (PG2, TX2, LT4) exert pro-inflammatory effects while those resulting from EPA and DHA (PG3, TX3, LT5) are less biologically active and have anti-inflammatory properties by opposing synthesis and activity of *n* – 6 PUFA-derived eicosanosids (EPA is the preferential substrate for LOX enzymes). Specialized pro-resolving mediators include lipoxins (LX), resolvins (Rv), protectins (Pr), and maresins (Mar). The resolvins were initially identified by their ability to promote the early resolution of the inflammatory cycle, hence the derivation of their names as resolvins; they are divided into two classes with the E-series resolvins (RvE1, RvE2, and RvE3) being synthesized from EPA and the D series resolvins (RvD1–RvD6) being derived from DHA. Upon acetylation of COX2 by low dose aspirin, the catalytic activity of COX2 gives rise to stereoisomers of these specific autocaoids; aspirin-triggered (AT) forms of LX, Rv and Pr (not shown) have been reported. Of note, through the blockade of the biosynthesis of pro-inflammatory prostaglandins from *n* – 6 PUFA, aspirin also reinforces the beneficial effects of *n* – 3 PUFA. HETE, hydroxy-eicosatetraenoic acid; HPETE, hydroperoxyl-eicosatetraenoic acid; HEPE, hydroxy-eicosapentaenoic acid; HDHA, hydroxy-docosahexaenoic; HPDHA, hydroperoxyl-docosahexaenoic.

eicosanoids, namely resolvin D1 (RvD1), RvD2 or RvE1 (Fig. 3) that facilitate clearance of debris via macrophage phagocytosis; this antitumor activity of resolvin is receptor-dependent since the effects of RvD1, RvE1 or RvD2 were lost in RvD1 receptor (ALX/FPR2), RvE1 receptor (ChemR23/ERV) and RvD2 receptor (GPR18/DRV2) knockout mice, respectively. The same group expanded on the above findings to document that aspirin-triggered resolvins (AT-RvDs) mediate the antitumor activity of aspirin [35]. Significantly, aspirin induction of tumor cell death was determined to be tumor stroma-dependent. These authors also showed that treatment of mice with AT-RvDs (e.g. AT-RvD1 and AT-RvD3) or lipoxin AT-LXA4 could inhibit primary tumor growth by enhancing macrophage phagocytosis of tumor cell debris. These studies provide indirect evidence that a large part of anticancer effects of $n-3$ PUFA may derive from their capacity to act as precursors of anti-inflammatory (aspirin-triggered) specialized proresolving mediators.

CONCLUSION

The multiple biological roles of lipids make FA nondispensable for proliferating cancer cells. However, although lipogenesis including FAS and MUFA generation support tumor growth, PUFA may exert tumor growth inhibitory effects. This view obviously requires nuances and increasing evidence proves for instance that FA may (instead of being synthesized) be captured from the extracellular medium to support cancer progression or that PUFA dietary supplementation is not necessarily associated with better outcomes for cancer patients. Today, this knowledge in the FA biology in cancer allows to envision new therapeutic strategies, from the targeting of lipid-addicted tumor compartment to the administration of eicosanoids instead of their

PUFA precursors, possibly together with low-dose aspirin.

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Conflicts of interest

There are no conflicts of interest.

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